












Journal of Management Inquiry 22(4) 399-414

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	L38:	(0)
	L39:	(93)
	L40:	(2)
	L41:	(0)
	L42:	(2)
	L43:	(5)
	L44:	(604)
	L45:	(4)
	L46:	(4)

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A wide variety of therapeutic and/or diagnostic agents may also be incorporated into the aqueous lipid suspension phase simply by adding the desired therapeutic or diagnostic agents to that phase. Suitable therapeutic and diagnostic agents, and suitable amounts thereof, will be readily apparent to those skilled in the art, once armed with the present disclosure. These agents may be incorporated into or onto the lipid membranes, or encapsulated in the resultant liposomes.

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	U	1	Document ID	Issue Dat	Page	Title	Current	Current	Retr	Inve
1	<input type="checkbox"/>	<input type="checkbox"/>	US 6416740 B1	20020709	62	Acoustically active drug delivery systems	424/9.52	424/450; 424/9.5;		Unger, Evar
2	<input type="checkbox"/>	<input type="checkbox"/>	US 6146657 A	20001114	24	Gas-filled lipid spheres for use in diagnostic and	424/450	424/489; 424/502;		Unger, Evar
3	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5846517 A	19981208	46	Methods for diagnostic imaging using a renal	424/9.52			Unger, Evar
4	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5817017 A	19981006	13	Medical devices and materials having enhanced	600/433	424/9.3; 600/420		Young, Stua al.

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1	L38:	(0)
2	L39:	(93)
3	L40:	(2)
4	L41:	(0)
5	L42:	(2)
6	L43:	(5)
7	L44:	(604)
8	L45:	(4)
9	L46:	(4)

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To further improve the magnetic effect of the resultant gas-filled liposomes for MRI, for example, one or more MRI contrast enhancing agents, such as paramagnetic or superparamagnetic contrast enhancing agents, may be added. Useful MRI contrast enhancing agents include paramagnetic ions such as transition metals, including iron (Fe.sup.+3), copper (Cu.sup.+2), and manganese (Mn.sup.+2) and the lanthanides such as gadolinium (Gd.sup.+3) and dysprosium (Dy.sup.+3), nitroxides, iron oxides (Fe.sub.3 O.sub.4), iron sulfides and paramagnetic particles such as manganese (Mn.sup.+2) substituted hydroxyapatites. As well, agents such as chromium (Cr.sup.+3), nickel (Ni.sup.+2), cobalt (Co.sup.+2) and europium (Eu.sup.+2) are other examples of

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	U	I	Document ID	Issue Dat	Page	Title	Current	Current	Retr	Inve
1	<input type="checkbox"/>	<input type="checkbox"/>	US 6416740 B1	20020709	62	Acoustically active drug delivery systems	424/9.52	424/450; 424/9.5;		Unger, Evar
2	<input type="checkbox"/>	<input type="checkbox"/>	US 6146657 A	20001114	24	Gas-filled lipid spheres for use in diagnostic and	424/450	424/489; 424/502;		Unger, Evar
3	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5846517 A	19981208	46	Methods for diagnostic imaging using a renal	424/9.52			Unger, Evar
4	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5817017 A	19981006	13	Medical devices and materials having enhanced	600/433	424/9.3; 600/420		Young, Stue al.

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L11: (13341) (n

L12: (207) 10

L13: (38) 12 ar

L14: (5960) ((

L15: (234) 14

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L17: (138) 16

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L21: (67) 20 ar

L22: (44) 21 ne

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Brief Summary Text - BSTX (6):

Rembaum (U.S. Pat. No. 4,267,234) refers to magnetic polyglutaraldehyde microparticles which are prepared by suspension polymerization in the presence of magnetic particles. Widder and Senyei (U.S. Pat. No. 4,247,406) prepare microparticles from an amino acid-polymer matrix in which magnetic particles are embedded. A similar method with nanoparticles is used by Schroder and Mosbach (WO 83/01738) whereby a crystalline hydrocarbon matrix surrounds the magnetic material. Groman and Josephson (U.S. Pat. No. 4,770,183) use magnetic metal oxide particles which are non-coated and coated with a polysaccharide and/or protein coating. Molday (U.S. Pat. No. 4,452,773) describes the synthesis of ferromagnetic iron oxide cores with a polysaccharide coating. He achieves a stable sol and can couple proteins to the dextran coating using periodate activation.

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	U	I	Document ID	Issue Dat	Pag	Title	Current	Current	Retr	In
22	<input type="checkbox"/>	<input type="checkbox"/>	US 5427767 A	19950627	13	Nanocrystalline magnetic iron oxide particles-method	424/9.32	424/9.32		Kresse, M
23	<input type="checkbox"/>	<input type="checkbox"/>	US 5342608 A	19940830	15	Gas containing contrast agent particles having	424/9.52	252/62.5		Moriya, T
24	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5336762 A	19940809		Polychelating agents for image and spectral	534/16	424/9.32		Ranney, D
25	<input type="checkbox"/>	<input type="checkbox"/>	US 5328681 A	19940712	16	Composition comprising magnetic metal oxide	424/9.32	252/62.5		Kito, Kyo
26	<input type="checkbox"/>	<input type="checkbox"/>	US 5315997 A	19940531	5	Method of magnetic resonance	600/420	424/9.34		Widder, K

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WO 83/11154 = 9,651,007
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L51: (1) chromium, gadolinium, iron, manganese, ferrites, and magnetite are also
L52: (1) contemplated, as are imageable compounds linked to or incorporated with
L53: (77) dextran, albumin, latex, polystyrene, or other particulate materials of
L54: (77) appropriate size.
L55: (18)
L56: (218) Brief Summary Text - BSTX (57):
L58: (6) In addition to iodinated or brominated materials, a number of other
L59: (3) electron-dense materials can be used in the present invention. The electron
L60: (141) density can be provided by non-radioactive elements or compounds such as gold
L61: (141) or iron, chromium, gadolinium, yttrium, zirconium, hafnium, tin or antimony as
L63: (120) oxides, phosphates, sulfides, or silicates, as well as other nonradioactive
L64: (1) metals. The foregoing can advantageously be utilized in the form of colloids
L62: (97) or particles of appropriate size.
L65: (119)
L57: (24) Current US Original Classification - CCOR (1):
424/9.322

	U	1	Document ID	Issue Dat	Page	Title	Current	Current	Retr	In
12	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5925752 A	19990720		Process for the preparation of macrocyclic chelants and	540/474	424/9.363;		Ripa, Gio
13	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5773024 A	19980630	25	Container with multi-phase composition for use in	424/450	424/43; 424/45;		Unger, Ev
14	<input type="checkbox"/>	<input type="checkbox"/>	US 5496536 A	19960305	11	Percutaneous lymphography	424/9.322	424/9.37;		Wolf, Ger
15	<input type="checkbox"/>	<input type="checkbox"/>	US 5336762 A	19940809		Polychelating agents for	534/16	424/9.32		Ranney, D

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Detailed Description Text - DETX (42):

Besides diamagnetic T2 contrast agents, the polymeric shells of the invention can be used as ferromagnetic or paramagnetic magnetic resonance contrast agents. These agents introduce a local magnetic field where they are present and consequently change the relaxation properties of the protons that are nearby. This change in proton T1 and T2 allows for these contrast agents to be used in the typical proton analysis. Most often a T1 weighted proton imaging sequence is used. Encapsulation of small ferromagnetic or superparamagnetic metal particles (e.g., Fe, Mn, and the like) into the polymeric shells enable this to be used as a contrast agent. For example, small (3 to 10 nm) particles of iron oxide can be dispersed in a fluorocarbon (or soybean oil, or other suitable medium) and then entrapped within a polymeric shell according to the present invention.

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	U	1	Document ID	Issue Dat	Pag	Title	Current	Current	Retr	In
36	<input type="checkbox"/>	<input type="checkbox"/>	US 5505932 A	19960409	21	Method for the preparation of fluorocarbon-containing	424/9.3	424/9.32 2;		Grinstaff al.
37	<input type="checkbox"/>	<input type="checkbox"/>	US 5370901 A	19941206	11	Compositions for increasing the image contrast in	427/2.12	424/9.5; 427/2.14		Tournier,
38	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5225282 A	19930706	9	Biodegradable magnetic microcluster comprising	428/407	252/62.5 4;		Chagnon, al.
39	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5120527 A	19920609	10	Paramagnetic oil emulsions as MRI contrast agents	424/9.36	424/535; 424/9.36		Li, King et al.

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L22: (44) 21 no

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phospholipid) of the type also suitable for controlled extended release of active compounds (WO-9107171); liposomes sequestered in gel (U.S. Pat. No. 4,708,861); metal chelates bound to liposomes, also suitable for use as MR contrast agents (WO-9114178); lipid complexes of X-ray contrast agents (WO-8911272); liposomes which can capture high solute to lipid ratios (WO-9110422); liposomes containing covalently bound PEG moieties on external surface to improve serum half-life (WO-9004384); contrast agents comprising liposomes of specified diameter encapsulating paramagnetic and/or superparamagnetic agents (WO-9004943); liposomes of the type also suitable for delivering imaging agents to tumours consisting of small liposomes prepared from pure phospholipids (EP-179444); encapsulated X-ray contrast agents such as iopromide in liposomes (U.S. Pat. No. 5,110,475); non-phospholipid liposome compositions (U.S. Pat. No. 5,043,165 and U.S. Pat. No. 5,049,389); hepatocyte-directed vesicle delivery systems (U.S. Pat. No. 4,603,044); gas-filled liposomes of the type also suitable as ultrasound contrast agents

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	U	1	Document ID	Issue Dat	Page	Title	Current	Current	Retr	In
2	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 6569451 B1	20030527		Targeted polymerized liposome diagnostic and	424/450	424/1.21		Li, King
3	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 6548047 B1	20030415		Thermal preactivation of gaseous precursor filled	424/9.51	424/450; 424/9.4;		Unger, Ev
4	<input type="checkbox"/>	<input type="checkbox"/>	US 6540981 B2	20030401	16	Light imaging contrast agents	424/9.6	424/9.1		Klaveness
5	<input type="checkbox"/>	<input type="checkbox"/>	US 6521211 B1	20030218	96	Methods of imaging and treatment with targeted	424/9.52	424/450; 424/9.5;		Unger, Ev
6	<input type="checkbox"/>	<input type="checkbox"/>	US 6479033 B1	20021112	17	Antitumor cystostatic and	424/9.32	424/450;		Reszka, R

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Liposomes encapsulating solid and liquid contrast enhancing agents are also encompassed within the subject invention. As used herein, the terms "solid contrast enhancing agent" and "liquid contrast enhancing agent", denotes solid particulate materials, and solubilized or liquid materials, respectively, which are echogenic on ultrasound. Suitable solid contrast enhancing agents will be readily apparent to those skilled in the art once armed with the present disclosure, and include magnetite (Fe.sub.3 O.sub.4), solid iodine particles such as particles formed from iodipamide ethyl ester, and particles formed by precipitating a water insoluble derivative of the ionic iodinated contrast medium metricate. Suitable liquid contrast enhancing agents will be readily apparent to those skilled in the art, once armed with the present disclosure, and include solubilized iodinated contrast agents. The latter is preferably used as an intravascular contrast agent for the purpose of visualizing flow, but is also highly effective for detecting tumors in the liver and spleen.

	U	I	Document ID	Issue Dat	Pag	Title	Current	Current	Retr	In
18	<input type="checkbox"/>	<input type="checkbox"/>	US 5123414 A	19920623	20	Liposomes as contrast agents for ultrasonic imaging and	600/431	264/4.1; 264/4.3;		Unger, Ev
19	<input type="checkbox"/>	<input type="checkbox"/>	US 5088499 A	19920218	20	Liposomes as contrast agents for ultrasonic imaging and	424/9.51	424/44; 424/450;		Unger, Ev
20	<input type="checkbox"/>	<input type="checkbox"/>	US 5045304 A	19910903	5	Contras agent having an imaging agent coupled to	424/9.32	424/646; 424/647;		Schneider al.
21	<input type="checkbox"/>	<input type="checkbox"/>	US 4849210 A	19890718	5	Magnetic resonance imaging of liver and spleen with	424/9.32 2	436/173; 436/526;		Widder, K

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Detailed Description Text - DETX (47):

In addition to lipids, other materials that may be used to form the microspheres include, for example, proteins such as albumin, synthetic peptides such as polyglutamic acid, and linear and branched oligomers and polymers of galactose, glucose and other hexosaccharides and polymers derived from phosphorylated and sulfonated pentose and hexose sugars and sugar alcohols. Carbohydrate polymers such as alginic acid, dextran, starch and HETA starch may also be used. Other natural polymers, such as hyaluronic acid, may be utilized. Synthetic polymers such as polyethyleneglycol, polyvinylpyrrolidone, polylactide, polyethyleneimines (linear and branched), polyionenes or polyiminocarboxylates may also be employed.

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	U	I	Document ID	Issue Dat	Page	Title	Current	Current	Retr	In
25	<input type="checkbox"/>	<input type="checkbox"/>	US 5846517 A	19981208	46	Methods for diagnostic imaging using a renal	424/9.52			Unger, Ev
26	<input type="checkbox"/>	<input type="checkbox"/>	US 5770222 A	19980623	54	Therapeutic drug delivery systems	424/450	264/4.1; 264/4.3;		Unger, Ev
27	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5733572 A	19980331		Gas and gaseous precursor filled microspheres as	424/450	424/1.21		Unger, Ev
28	<input type="checkbox"/>	<input type="checkbox"/>	US 5585112 A	19961217	47	Method of preparing gas and gaseous precursor-filled	424/450	264/4.1; 264/4.3;		Unger, Ev
29	<input type="checkbox"/>	<input type="checkbox"/>	US 5567413 A	19961022	17	Flexible amphiphilic microbubbles for ultrasound	424/9.51	424/450; 424/9.52		Klaveness
30	<input type="checkbox"/>	<input type="checkbox"/>	US 5536490 A	19960716	14	Contrast agents	424/9.52	424/9.51		Klaveness

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Drawing Description Text - DRTX (114):

The lipid, protein, polymer, and/or vesicle compositions of the present invention, and especially the vesicle compositions, may serve not only as effective carriers of the superparamagnetic agents described above, but also may improve the effect of the susceptibility contrast agents.

Superparamagnetic contrast agents include metal oxides, particularly iron oxides but including manganese oxides, and as iron oxides, containing varying amounts of manganese, cobalt and nickel which experience a magnetic domain. These agents are nano or microparticles and have very high bulk susceptibilities and transverse relaxation rates. The larger particles, for example, particles having diameters of about 100 nm, have much higher R2 relaxivities as compared to R1 relaxivities. The smaller particles, for

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	U	I	Document ID	Issue Dat	Page	Title	Current	Current	Retr	In
25	<input type="checkbox"/>	<input type="checkbox"/>	US 5846517 A	19981208	46	Methods for diagnostic imaging using a renal	424/9.52			Unger, Ev
26	<input type="checkbox"/>	<input type="checkbox"/>	US 5770222 A	19980623	54	Therapeutic drug delivery systems	424/450	264/4.1; 264/4.3;		Unger, Ev
27	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5733572 A	19980331		Gas and gaseous precursor filled microspheres as	424/450	424/1.21		Unger, Ev
28	<input type="checkbox"/>	<input type="checkbox"/>	US 5585112 A	19961217	47	Method of preparing gas and gaseous precursor-filled	424/450	264/4.1; 264/4.3;		Unger, Ev
29	<input type="checkbox"/>	<input type="checkbox"/>	US 5567413 A	19961022	17	Flexible amphiphilic microbubbles for ultrasound	424/9.51	424/450; 424/9.52		Klaveness
30	<input type="checkbox"/>	<input type="checkbox"/>	US 5536490 A	19960716	14	Contrast agents	424/9.52	424/9.51		Klaveness

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The gas filled microspheres used in the present invention may not only serve as effective carriers of the superparamagnetic agents, e.g., iron oxides, but also appear to magnify the effect of the susceptibility contrast agents. Superparamagnetic contrast agents include metal oxides, particularly iron oxides but including manganese oxides, and as iron oxides, containing varying amounts of manganese, cobalt and nickel which experience a magnetic domain. These agents are nano or microparticles and have very high bulk susceptibilities and transverse relaxation rates. The larger particles, e.g., 100 nm diameter, have much higher R2 relaxivities than R1 relaxivities but the smaller particles, e.g., 10 to 15 nm diameter have somewhat lower R2 relaxivities, but much more balanced R1 and R2 values. The smallest particles, e.g., monocrystalline iron oxide particles, 3 to 5 nm in diameter, have lower R2 relaxivities, but probably the most balanced R1 and R2 relaxation rates. Ferritin can also be formulated to encapsulate a core of very high relaxation rate superparamagnetic iron. It has been discovered that stabilized gas-filled

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23	<input type="checkbox"/>	<input type="checkbox"/>	US 5922304 A	19990713	47	Gaseous precursor filled microspheres as magnetic	424/9.3	424/9.32		Unger, Ev
24	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5853752 A	19981229		Methods of preparing gas and gaseous precursor-filled	424/450	264/4.1; 264/4.3;		Unger, Ev
25	<input type="checkbox"/>	<input type="checkbox"/>	US 5846517 A	19981208	46	Methods for diagnostic imaging using a renal	424/9.52			Unger, Ev
26	<input type="checkbox"/>	<input type="checkbox"/>	US 5770222 A	19980623	54	Therapeutic drug delivery systems	424/450	264/4.1; 264/4.3;		Unger, Ev
27	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5733572 A	19980331		Gas and gaseous precursor	424/450	424/1.21		Unger, Ev

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A gas filled vesicle filled with oxygen gas should create extensive free radicals with cavitation. Also, metal ions from the transition series, especially manganese, iron and copper can increase the rate of formation of reactive oxygen intermediates from oxygen. By encapsulating metal ions within the vesicles, the formation of free radicals in vivo can be increased. ~~These metal ions may be incorporated into the liposomes as free salts, as complexes e.g., with EDTA, DTPA, DOTA or desferrioxamine, or as oxides of the metal ions.~~ Additionally, derivatized complexes of the metal ions may be bound to lipid head groups, or lipophilic complexes of the ions may be incorporated into a lipid bilayer, for example. When exposed to thermal stimulation, e.g., cavitation, these metal ions then will increase the rate of formation of reactive oxygen intermediates. Further, radiosensitizers such as metronidazole and misonidazole may be incorporated into the gas filled vesicles to create free radicals on thermal stimulation.

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	U	1	Document ID	Issue Dat	Page	Title	Current	Current	Retr	In
9	<input type="checkbox"/>	<input type="checkbox"/>	US 6416740 B1	20020709	62	Acoustically active drug delivery systems	424/9.52	424/450; 424/9.5;		Unger, Ev
10	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 6403056 B1	20020611		Method for delivering bioactive agents using	424/9.51	424/400; 424/450;		Unger, Ev
11	<input type="checkbox"/>	<input type="checkbox"/>	US 6315981 B1	20011113	42	Gas filled microspheres as magnetic resonance imaging	424/9.32 3	424/450; 424/9.3;		Unger, Ev
12	<input type="checkbox"/>	<input type="checkbox"/>	US 6231834 B1	20010515	75	Methods for ultrasound imaging involving the use of	424/9.51	424/9.52 ;		Unger, Ev
13	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 6159445 A	20001212	16	Light imaging contrast	424/9.6	424/9.1;		Klaveness

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Detailed Description text = DEIX (18):
Solid particulate matter which produces contrast-type enhanced images include graphite particles, glass beads, and similar substances. The present invention has grossly examined many of the available solid particulate matter which theoretically may be used as a contrast agent, and has determined that one such agent, although not previously disclosed as a contrast agent, has a number of very desirable properties. Such agent and associated liquid carriers are broadly disclosed in U.S. Pat. No. 4,247,406 the disclosure which is herein incorporated by reference. In the '406 patent, the solid particulate material comprises magnetically localizable, biodegradable carriers which comprise microspheres formed from an amino acid polymer matrix with magnetic particles embedded therein. For example, albumin can be used as the matrix material and magnetite (Fe.sub.3 O.sub.4) can be used as the magnetic particles. The microspheres have an average diameter of less than 1.5 microns and the magnetic particles contained therein have an average size of not more than 1 000 Angstroms. The microspheres may contain from 50 to 350 parts by

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	U	I	Document ID	Issue Dat	Pag	Title	Current	Current	Retr	In
37	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 4849210 A	19890718		Magnetic resonance imaging of liver and spleen with	424/9.32	436/173;		Widder, K
38	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 4675173 A	19870623		Method of magnetic resonance imaging of the liver and	424/9.32	252/62.5		Widder, K
39	<input type="checkbox"/>	<input type="checkbox"/>	US 4572203 A	19860225	8	Contact agents for ultrasonic imaging	424/9.52	424/9.5;		Feinstein
40	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 4460560 A	19840717		Drug delivery by polymeric carriers	424/1.37	424/450;		Tokes, Zo
								424/493;		al.

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